Address correspondence to M. Milinski. E-mail: milinski@mpil-ploen.mpg.de.

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Wondering about sex: W. D. Hamilton's contribution to explaining nature's masterpiece

Paul Schmid-Hempel
ETH Zürich, Experimental Ecology, ETH-Zentrum NW, CH-8092 Zürich, Switzerland

Sexual reproduction, or sex for short, is an extremely successful breeding strategy. With some exceptions, metazoan organisms use sex, and even among protozoans or bacteria, some forms of sex exist, defined by its consequence of gene exchange (Bell, 1982). Yet, theory has so far failed to provide a universal and satisfactory explanation for the adaptive advantages of sex in Darwinian terms. This question captured William D. Hamilton's imagination for some 20 years, starting in the mid-1970s. His answer traces back to Haldane (1949) and was critically stimulated by George C. Williams (1975). In Hamilton's view, short-term advantages resulting from antagonistic coevolution by parasites favors sex, despite its inherent cost as compared to the asexual (parthenogenetic) alternative.

An annoying consequence of sex is visible in a well-known myth. When Noah loaded his ark, he took two individuals of each species—one male and one female—on board. Given the limited carrying capacity of his ark, Noah clearly had to accept a twofold cost of sex. Indeed, sexual species are forced to produce males in addition to females. If males were equally costly to produce, this requires that half of the resources available for breeding have to be invested in males whose only function is to fertilize the daughters. In most species, males provide little parental effort. To make matters worse, and as a consequence of having males, any one offspring that a female produces receives only half of her genes, the other half being from her mate. Although the precise definition often varies between students of the problem, there is such a thing as a "twofold cost" of sex compared to the asexual alternative (Maynard Smith, 1978). Bell (1982) defined sex by its aspects of mixis and syngamy, that is, the merging of genetic information, generally from different sources, into a single offspring. Sex is therefore conceptually different from reproduction because it changes the genetic state of the cell rather than the number of cells as happens with reproduction (Bell, 1982). We nevertheless speak of "sexual reproduction" because in higher organisms these two processes have become inextricably linked. This is not the end of the dilemma, however. Recombination of genes is a major defining feature of mixis and syngamy in higher organisms. Recombination universally breaks up gene combinations and therefore destroys a successful genotype that has, in fact, managed to survive and is now able to reproduce. The combination of these adversities makes the adaptive value of sex hard to explain.

Fisher (1930) realized that sexual reproduction, in particular the process of genetic recombination, leads to an increase in the genetic variance among offspring. According to his fundamental principle of natural selection, the rate of evolution is directly proportional to the extant amount of (additive) genetic variance present in a population. Therefore, sexual populations can respond to selection faster than asexual populations. Another way to put it is that sex and recombination allows allocating independently arising favorable mutants to one offspring much more efficiently. Asexuals have to wait for these independent mutations to occur one after another in the same lineage in order to find them combined in a single offspring (the "Fisher-Muller model"). This long-term advantage for a sexual population, so Fisher (1930) argued, favors sex and makes it spread and be maintained against the asexual alternative over long periods of time. This paradigm, which in essence was also shared by August Weismann and Hermann Muller, remained very much unchallenged for nearly 30 years. However, in the rebellious climate of the 1960s, evolutionary biologists started to doubt the validity of arguments based on long-term benefits for entire sets of individuals. Indeed, Crow and Kimura (1965, 1969) realized that Weismann, Muller, and Fisher all relied on group selection to explain sexual reproduction.

Group selection arguments of the kind postulated by Fisher (1930) were diametrically opposed to Hamilton's (1964) concept of kin selection and the implied process of direct, short-term benefits for alternative genetic information. From his own work on extreme sex ratios in a variety of insect species [e.g., fig wasps (Hamilton, 1967)], Hamilton could see that in small, localized and therefore inbred populations, the consequences of sex for recombination are more or less eliminated. At the same time, females in such populations can easily reduce their production of males and thus avoid some of the costs of sex without compromising efficient reproduction.

Against this background of his dissatisfaction with existing explanations, Hamilton was asked to review two books that both appeared in 1975: Michael T. Ghiselin's *The Economy of*

Nature and the Evolution of Sex and George C. Williams's *Sex and Evolution*. While he had some reservations against Ghiselin's treatment, Hamilton found himself in natural agreement with William's stance that ''sex must be shown to be advantageous to the individual sexist, not just to population or species as a whole'' (Hamilton, 1975: 175). In particular, Hamilton made the remarkable statement that

> it seems to me that [to explain sex] we need environmental fluctuations around a trend line of change. For the source of these we may look to fluctuations and periodicities inherent in our solar system, *and also to the possibility of others generated by life itself*. The latter line of thought tends to carry us back from the egg of sex to the hen of a multispecies system. (Hamilton, 1975: 180 [emphasis added])

Here, the kernel of the idea of antagonistic coevolution becomes visible, although, at the time, Hamilton did probably not think of parasites as the major cause.

This seemed to have changed radically over the following years and took shape in his landmark paper on ''Sex vs. Non-sex vs. Parasites'' (Hamilton, 1980). There, the idea of negative frequency-dependent selection caused by coevolving parasites is spelled out in mathematical terms and shown to be able to favor sexual over asexual reproduction, at least under some conditions. In this scenario, rare host genotypes have an advantage because they offer only a small target to the generally more rapidly evolving parasites. An implicit requirement is that parasites and their hosts match up to some degree. In other words, a parasite type can only infect one or a few host types, while hosts are susceptible to some but not all parasite types. This matching must reflect some genotypic variation in the host (and parasite, for that matter) because genotypic variation is what is affected by sex. In any case, when rare host genotypes have an advantage, rare host types must increase in numbers. At some point, this inevitably leads to the loss of their advantage due to rarity, and the parasites will now have ample opportunities to catch up on this common host and increase in numbers. Some time later still, the formerly rare host genotypes have become heavily infested by their coevolving parasites and will be at a disadvantage. These hosts will therefore start to decline in numbers, until they have reached their former status of a rare but fit genotype. In the meantime, other host (and parasite) genotypes have also gone through this co-evolutionary cycle. The time lag between the change in the host frequencies and the capacity of parasites to respond by numbers causes host and parasite genotypes to track each other over time. This scenario can create persistent cycles, albeit of irregular shape, with characteristics depending on the exact conditions. More importantly for our discussion, mothers that produce their offspring sexually are more likely to produce, by recombination, rare genotypes for their offspring than asexual mothers that have to wait for mutations to do the same. Therefore, sexual mothers are more likely to have offspring that escape the currently prevailing parasite types—the immediate advantage for the individual sexist that Hamilton was looking for (Hamilton, 1993; Hamilton et al., 1990).

It often happens that, at certain times during the history of a science, new ideas are somehow in the air. This was the case for the problem of sex in the mid-1970s. For example, Levin (1975), considering pest pressures on plants, proposed that recombination, preventing the congealing of the genome into a single linkage group, was selected for by persistent tracking of plant hosts by multiple pathogens and herbivores. A decisive element in the discussion was added by Clarke (1976) and Jaenike (1978) by pointing out that recombination is probably not advantageous simply because it produces new genotypes in offspring but because it generates rare genotypes. This is the essential idea of negative frequency-dependent selection whereby the rare genotypes have a high fitness and the common ones a low fitness. It was Hamilton who fleshed out these ideas in the way we discuss them today.

Van Valen (1973) realized that the geometric distribution of life spans of species, genera, and families over geological time spans, as inferred from palaeontological records, defied any simple notion of how accumulating effects of some kind (i.e., some form of ''senescence'') could lead to the ultimate death of a species. Rather, such a time-independent risk of extinction could be much more convincingly explained by assuming an ongoing coevolutionary arms race between a species and its competitors and enemies. This is very much like Alice's attempts to follow the Red Queen in *Through the Looking Glass* by running as fast as she can just to discover that both still are at the same place. When Van Valen (1973) used this analogy he did not think so much of parasites in this context. Bell (1982) connected this term to the explanation of sex and especially referred to the temporal dynamics of coevolving hosts and parasites, in contrast to the spatial aspect of among-offspring competition (which he called the ''tangled bank''). It is interesting that the implications of the original Red Queen metaphor of Van Valen (1973) and the concept of Bell (1982) are actually quite different. In the coevolutionary race envisaged by Van Valen, species evolve in some direction—for example, toward harder shells in mussels and bigger claws in crabs. The essential feature of host–parasite coevolution, however, is the reuse of genetic information without any apparent evolutionary direction (Hamilton et al., 1990). Therefore, viewed from the outside, species may not appear to evolve at all, while behind this Potemkinian facade there is a violent turnover and recycling of genes as parasites chase their hosts through the genotype space.

Hamilton developed his ideas further in the early 1980s. He used a combination of analytical treatment and computer evaluations to consider explicit models for the evolution of sex (Hamilton, 1980). Essentially similar conclusions were also derived in a later study (Hamilton et al., 1981). In these studies, a major problem had to be discussed, too. At the time, models showed that the best conditions for the spread of sex were found when parasites exert strong, truncating selection and hosts have high fecundity. However, these are not the most obvious correlates of sex in nature. Indeed, sexual species typically have low fecundities; that is, they are species of large body size and extensive parental care (such as humans), and most parasites do not kill but rather just debilitate the host. However, the analysis in Hamilton et al. (1981), and especially later in Hamilton et al. (1990) showed that such conditions are not prohibitive for sex to prevail.

Hamilton was deeply interested in a special property of the Red Queen scenario that can explain the maintenance of large amounts of genetic variation in natural populations by selection rather than neutrality. In fact, compared to rivaling hypotheses, such as the mutation-accumulation hypothesis (Kondrashov, 1982), the Red Queen-type coevolutionary scenario suggests that sexual populations stow away temporarily unfit genetic information for a while because such alleles are not eliminated but protected by negative frequency-dependent selection. These alleles necessarily become rare with time but can provide protection during the next, though occasional episode where the selective environment reverses its state (i.e., new types of parasites become common). Hence, whether sex spreads is affected more often by which genotypes occupy the lower end of the fitness scale rather than who occupies the higher end. This is a consequence of the fact that the long-term geometric mean fitness determines the fate of a sexual or asexual variant and not the arithmetic mean fitness. And here, sex fares better than asex, because, after a while, individuals in sexual populations can still generate a rare offspring genotype when the overall parasite pressure on

common types has become strong, whereas the asexual parents carrying the now needed alleles were eliminated (and can only be regenerated by the vastly slower process of mutation). Hence, despite a higher fitness that asexual variants can exploit by carrying the best alleles most of time, they are unlikely to persist through occasional crunch periods when severe parasite pressure against these successful types has built up. During these episodes, recombination furnishes the now advantageous combinations much more quickly than mutation does. As a side effect, Hamilton realized, genetic variation is maintained in the population.

Empirical support for the concept of a parasite-driven Red Queen process is difficult to gather, especially in field systems. The most convincing evidence so far comes from the New Zealand freshwater snail *Potamopyrgus antipodarium,* where a long-term study has provided evidence for a cost of sex (Jokela et al., 1997a), but also for the connection of sex with parasites (especially trematodes; Lively, 1989) and rare-genotype advantage (Lively and Dybdahl, 2000). At the same time, plausible alternative hypotheses could be eliminated (Jokela et al., 1997b; Lively et al., 1998). Nevertheless, Hamilton's theory for the evolution and maintenance of sex is not universally accepted and, in fact, is a matter of heavy dispute (e.g., Barton and Charlesworth, 1998). On the other hand, his vision assembles a number of disparate phenomena under one umbrella—for example, the combinatorial lock-and-key aspects of host defenses against parasites and the advantage of sex through recombination. The field is thus wide open to imaginative research.

Hamilton's vision extended beyond the simple consideration of the conditions for the evolution of sex. In fact, Hamilton formulated one of the most challenging statements during the Dahlem conference in Berlin in 1982, when he stated that "if the idea about parasites is right, species may be seen in essence as guilds of genotypes committed to free fair exchange of biochemical technology for parasite exclusion" (Hamilton, 1982: 271). How coevolution with parasites may promote speciation and how this process could maintain species boundaries remains a major challenge for the future (e.g., Breeuwer and Werren, 1995). Similarly, and perhaps more disturbingly, for behavioral ecologists, Hamilton et al. (1981: 363) found that "if sex is so important then our reliance on coefficients of relatedness in genetical kinship theory is placed in doubt: the coefficients of relatedness currently used fail to asses special advantages possessed by sexual progeny." Indeed, the special combinatorial (epistatic) properties generated by recombination may not be adequately captured by the average genetic relatedness between parents and offspring. If such epistatic effects are strong, as they might be during occasional periods of intensive selection by parasites, the nonlinearity in the selection profile generated by coevolving parasites can counteract kinship benefits. To cooperate with close kin is therefore both a boon and a bane (Baer and Schmid-Hempel, 1999).

There is little doubt that Hamilton's interest in the evolution of sex was a straightforward extension of his thinking on kin selection and on a range of other phenomena, such as skewed sex ratios, group formation, and migration. His unifying principle was that selection operates primarily on genes and over short time scales. While he always stressed that selection operates at any level and all the time, this principle gives selection for the benefit of groups, populations, or species much less weight most of the time. The application of this principle has made behavioral ecology a very successful branch of research. However, we should remind ourselves that Hamilton's legacy is much broader than a series of single concepts that address, for example, the evolution of sociality or sexual selection. Rather, thinking in populations, with their ecology and dynamics of genes, based on sound natural history, is at the heart of the matter to explain the adaptive value of behaviors, or, more generally, the adaptive value of decisions made by organisms in their environment. Whatever direction the field of behavioral ecology takes in the future, this essential distillate of Bill Hamilton's ideas will be with us for a long time to come.

I am grateful to Boris Baer, Curt Lively, and Jukka Jokela for discussions on Red Queens. My personal contacts with Bill Hamilton will always be fondly remembered.

Address correspondence to P. Schmid-Hempel. E-mail: psh@eco.umnw.ethz.ch.

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